

## Review Article

# Efficacy and safety of gemcitabine-targeted agent combination therapy in advanced pancreatic cancer: a meta-analysis of randomized controlled trials

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**Abstract:** Objective: A meta-analysis was performed to compare the clinical efficacy and safety of gemcitabine in combination with targeted agents versus gemcitabine alone in advanced pancreatic cancer (APC). Methods: PubMed, EMBASE and Cochrane Library databases were searched to find relevant clinical trials which were designed to investigate targeted agents in the treatment of APC patients (up to October 2017). The end-points included overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and toxicity rate. Publication bias was evaluated by Egger's test and funnel plots. Results: Twenty-eight trials involving a total of 8858 volunteers were selected for the meta-analysis. No significant difference was found in OS (HR = 0.969, 95% CI: 0.922-1.019,  $P = 0.217$ ) and ORR (OR = 1.053, 95% CI: 0.799-1.388,  $P = 0.714$ ) between targeted agents plus gemcitabine and gemcitabine alone. Targeted agents plus gemcitabine had significant but marginal benefit in PFS (HR = 0.923, 95% CI: 0.876-0.974,  $P = 0.003$ ) compared with gemcitabine alone. Targeted agents added to gemcitabine significantly increased the grade 3-4 neutropenia, thrombocytopenia, diarrhoea and rash compared with gemcitabine alone. The funnel plot presented substantial symmetry and showed little evidence of publication bias. Conclusions: Based on the outcomes of this analysis, addition of targeted agents to gemcitabine did not improve the OS and ORR of APC patients, and significantly but marginally increased their PFS. So the clinical efficacies of targeted agents need to be further investigated using other treatment strategies.

**Keywords:** Advanced pancreatic cancer, targeted agents, gemcitabine, overall survival, meta-analysis

## Introduction

In the United States, advanced pancreatic cancer (APC) is the fourth leading cause of cancer-related mortality [1], and it is estimated that total deaths of pancreatic cancer will increase dramatically to become the second leading cause of cancer-related death before 2030 [2]. In China, the statistics from the National Cancer Center showed that the incidence of pancreatic cancer ranked ninth, and the death rate ranked sixth in 2015 [3]. The 5-year survival of pancreatic cancer was 8% in 2016, and the morbidity and mortality of this cancer are continuous increasing around the world currently [4]. More than 80% of patients have already developed to locally advanced or metastatic pancreatic cancer when diagnosed [5]. As a result, majori-

ty of pancreatic cancer patients missed the surgery opportunity of removing the tumor.

Gemcitabine (GEM) is considered as a standard first-line chemotherapy that offers limited clinical benefits for APC patients [6]. In the attempt to increase overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) of APC patients, many clinical trials have been designed to evaluate the efficacy of GEM combination therapy [7]. Recently, some studies have demonstrated that combination chemotherapy obtained more clinical benefits than single agents. The albumin-bound paclitaxel plus GEM significantly improved OS (8.5 vs. 6.7 months;  $P < 0.001$ ) and PFS (5.5 vs. 3.7 months;  $P < 0.001$ ) compared with GEM alone [8]. Two meta-analyses showed the positive outcomes. one study by Zhang et al. reported

that GEM combined with a second cytotoxic agent significantly improved OS, PFS and ORR compared with GEM alone in APC patients [9]. Another study by Ciliberto et al. demonstrated that GEM plus chemotherapy (platinum, fluoropyrimidine, irinotecan, biotherapy and others) obtained a marginal benefit on OS compared with GEM alone in APC patients [10]. In addition, FOLFIRINOX (5-fluorouracil, irinotecan and oxaliplatin) increased significantly the OS (11.1 vs. 6.8 months;  $P < 0.001$ ) compared with GEM alone in APC patients [11]. Moreover, these combination treatment regimens were linked with increased adverse events.

At present, targeted therapy becomes a focus of cancer treatment, and it has brought great clinical benefits for patients with solid tumors, such as colorectal cancer, breast cancer, lung cancer [12-14]. One example is the orally administered targeted agent erlotinib, which inhibits the tyrosine kinase domain of epidermal growth factor receptor (EGFR) and has brought significant benefits on OS and PFS in patients with non-small-cell lung cancer [15, 16]. A study by Moore et al. reported that erlotinib plus GEM significantly increased the OS (6.24 vs. 5.91 months;  $P = 0.038$ ) and PFS (3.75 vs. 3.55 months;  $P = 0.004$ ) compared with GEM monotherapy for APC patients [17]. Bevacizumab is a recombinant humanized monoclonal antibody against vascular endothelial growth factor (VEGF). Bevacizumab plus chemotherapy resulted in great clinical values in advanced non-small-cell lung cancer and advanced colorectal cancer [18, 19], but can't bring the value for APC patients [20]. Axitinib is a potent and selective second-generation inhibitor of VEGF receptors, and can prolong the PFS of the patients with advanced renal cell carcinoma compared with sorafenib [21], but did not improve the survival of APC patients [22]. A study by Borad et al. reported that TH-302 (a kind of hypoxia-activator) plus GEM improved significantly the PFS of APC patients [23]. Among the targeted drugs, only erlotinib and TH-302 showed a significant clinical benefits for APC patients [17, 23, 24].

Some randomized clinical trials (RCTs) were designed to evaluate the efficacy and safety between GEM alone and GEM plus targeted agents (GEM + TA), but the conclusions were

still disputed. Therefore, we undertook a meta-analysis to comprehensively evaluate the clinical outcomes of eligible RCTs.

### Methods

#### *Search strategy*

The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) criteria was applied to perform this meta-analysis [25]. Two authors (Xinyan Li and Weichen Li) searched the PubMed, EMBASE, and Cochrane Library databases for relevant articles (up to October 2017). The search used the terms "pancreatic", "pancreas", "targeted", and "gemcitabine". Meanwhile, references cited in the selected articles were also checked for finding the potential articles.

#### *Selection criteria*

The included trials in the meta-analysis must meet the following criteria: 1) the studies were prospective and randomized trials; 2) the patients were diagnosed as APC (including locally advanced and/or metastatic pancreatic cancer); 3) the control arm received GEM, while the treatment arm received GEM + TA; 4) the primary end-points were OS and PFS, the secondary end-points were ORR and toxicity rates.

#### *Data extraction*

Two independent authors (Xinyan Li and Weichen Li) assessed the abstracts of searched studies. If one author deemed that an abstract was eligible, the full text of the study was read carefully for further assessment by two investigators. Any disagreements were discussed with other senior specialist. The following data were extracted: the first author, publication year, number of patients enrolled, regimens, median age of patients, gender ratio, types of action mechanisms, outcomes of efficacy and safety.

#### *Validity assessment of the included studies*

The qualities of selected studies were assessed in five aspects (random method, allocation concealment, blind method, withdraw description, identical baseline) according to The Cochrane Handbook for Systematic Reviews of Interventions [26].

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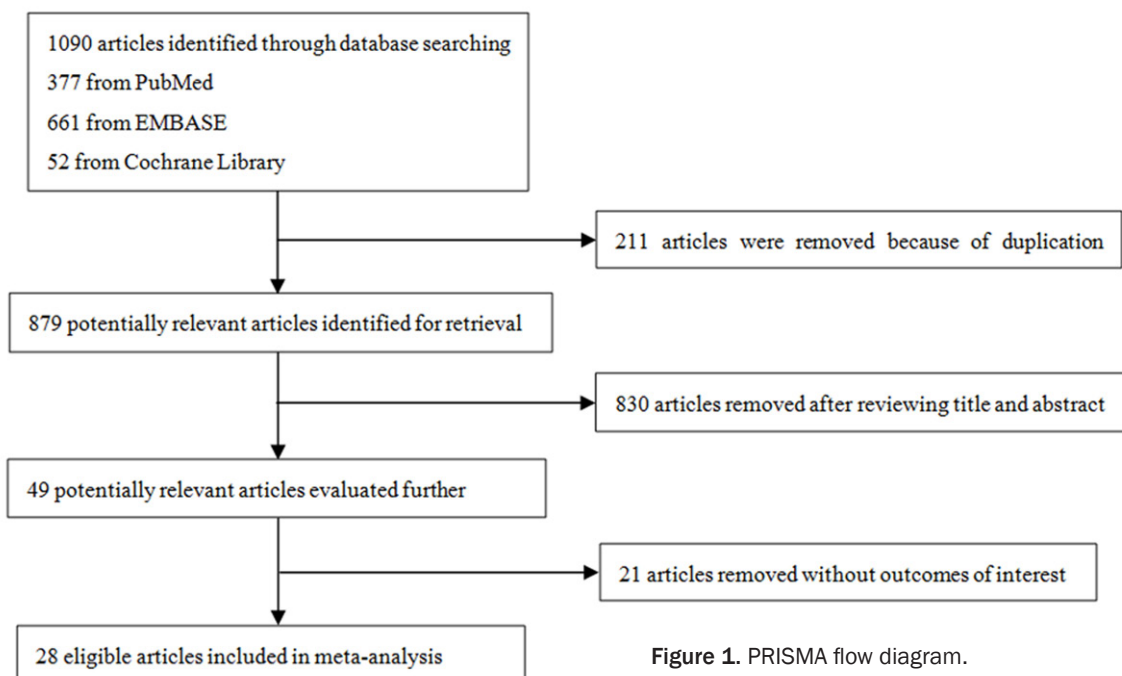


Figure 1. PRISMA flow diagram.

### Statistical analysis

The meta-analysis was performed by using the software Stata 12.0 (Stata\_Corporation, Texas, USA). Pooled hazard ratios (HRs) with 95% confidence intervals (CIs) were applicable in OS and PFS. The outcomes of ORR and adverse events were presented as pooled odds ratios (ORs) with 95% CIs. Heterogeneity across the studies was tested by using chi-squared test with a significance threshold of 0.05. A  $P$  value  $> 0.05$  indicates a lack of heterogeneity between the trials, and fixed effects model was used for meta-analysis. To the contrary, a  $P$  value  $< 0.05$  indicated that the studies were heterogeneous, and random effects model was selected. The selected trials included the targeted agents with different molecular targeted mechanism. Subgroup analysis, classified according to the types of action mechanisms, was performed for end-points. Publication bias was evaluated by using Egger's test and funnel plot [27]. For these analyses, a  $P$  value  $< 0.05$  was considered statistically significant.

### Results

#### Selection of the trials

The search strategy of individual studies is shown in a flow chart (Figure 1). A total of 1090

studies were found by the literature search. According to the selected criteria, 211 duplicate studies were removed initially, while 851 were excluded for unmet selection criteria. Finally, 28 eligible RCTs involving a total of 8858 patients were selected for meta-analysis [17, 20, 22-24, 28-50]. In the 28 trials, 13 trials were randomized Phase II trials and 15 trials were randomized Phase III trials. Five trials contained multiple arms comparison, and each comparison was investigated separately [23, 41, 42, 49, 50]. 15 kinds of targeted mechanisms were contained among these 28 trials. In our study, patients in the treatment arm received GEM + TA, and patients in the control arm received GEM monotherapy. Table 1 shows the main characteristics of the included trials.

#### Validity assessment of the included studies

According to the standard evaluation method, there were twenty-five trials A (low risk of bias), two trials B (intermediate risk of bias) and one trial C (high risk of bias) (Table 2).

#### Overall survival analysis

Twenty-three studies reported OS (HR with 95% CI). In the meta-analysis, the test for heterogeneity of OS reported no significant difference ( $P = 0.575$ ), therefore the fixed-effects model was

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**Table 1.** The main characteristics of the selected studies for meta-analysis

First author	Year	Phase	Arms (patients)	Types of targeted agent	Male %	Median age, y	Median OS	Median PFS	OS HR	PFS HR	LA/MPC, %
Friess [28]	2006	II	GEM + cilengitide (n = 46)	Angiogenesis inhibitor	57.0	68.0	6.7 months	3.6 months	NA	NA	7/93
			GEM (n = 43)		42.0	66.0	7.6 months	3.8 months		10/90	
Spano [29]	2008	II	GEM + axitinib (n = 69)	Angiogenesis inhibitor	51.0	65.0	6.9 months	4.2 months	0.71	0.79	42/58
			GEM (n = 34)		47.0	61.0	5.6 months	3.7 months		44/66	
Richards [30]	2011	II	GEM + enzastaurin (n = 86)	Angiogenesis inhibitor	53.5	68.3	5.6 months	3.4 months	NA	NA	10/90
			GEM (n = 44)		73.0	64.1	5.1 months	3.0 months		14/86	
Kindler [20]	2010	III	GEM + bevacizumab (n = 302)	Angiogenesis inhibitor	58.0	63.7	5.8 months	3.8 months	1.04	NA	16/84
			GEM (n = 300)		51.0	65.0	5.9 months	2.9 months		15/85	
Kindler [31]	2011	III	GEM + axitinib (n = 314)	Angiogenesis inhibitor	61.0	61.0	8.5 months	4.4 months	1.014	1.006	25/72
			GEM (n = 316)		59.0	62.0	8.3 months	4.4 months		23/72	
Gonçalves [32]	2012	III	GEM + sorafenib (n = 52)	Angiogenesis inhibitor	58.0	61.0	8.0 months	3.8 months	1.27	1.04	17/83
			GEM (n = 52)		62.0	64.0	9.2 months	5.7 months		23/77	
Rougier [33]	2013	III	Aflibercept (n = 271)	Angiogenesis inhibitor	59.0	62.0	6.5 months	3.7 months	1.165	1.018	0/100
			GEM (n = 275)		57.0	61.0	7.8 months	3.7 months		0/100	
Bergmann [34]	2015	II	GEM + sunitinib (n = 52)	Angiogenesis inhibitor	55.8	61.2	30.4 weeks	11.6 weeks	NA	NA	NA
			GEM (n = 54)		52.0	66.5	36.7 weeks	13.1 weeks		NA	
Ioka [22]	2015	III	GEM + axitinib (n = 314)	Angiogenesis inhibitor	60.8	61.0	8.5 months	4.4 months	1.014	1.006	24/76
			GEM (n = 316)		59.5	62.0	8.3 months	4.4 months		24/76	
Yamaue [35]	2015	II/III	GEM + elpamotide (n = 100)	Angiogenesis inhibitor	62.0	63.5	NA	3.7 months	0.87	NA	27/73
			GEM (n = 53)		59.0	65.0	NA	3.8 months		26/74	
Van Cutsem [36]	2004	III	GEM + tipifarnib (n = 341)	FTase inhibitor	57.0	61.0	193 days	112 days	1.03	1.03	24/76
			GEM (n = 347)		58.0	62.0	182 days	109 days		23/77	
Eckhardt [37]	2009	III	GEM + tipifarnib (n = 124)	FTase inhibitor	36.0	63.0	202 days	NA	1.07	NA	29/71
			GEM (n=120)		41.0	60.0	221 days	NA		27/73	
Senderowicz [24]	2007	III	GEM + erlotinib (n = 261)	EGFR inhibitor	49.0	NA	6.4 months	3.8 months	0.81	0.76	23/77
			GEM (n=260)		56.0	NA	6.0 months	3.5 months		24/76	
Moore [17]	2007	III	GEM + erlotinib (n = 285)	EGFR inhibitor	47.7	63.7	6.24 months	3.75 months	0.82	0.77	24/76
			GEM (n = 284)		57.0	64.0	5.91 months	3.55 months		25/75	
Philip [38]	2010	III	GEM + cetuximab (n = 372)	EGFR inhibitor	51.0	63.7	6.3 months	3.4 months	1.06	1.07	21/79
			GEM (n = 371)		54.0	64.3	5.9 months	3.0 months		22/78	
Propper [39]	2014	II	GEM + erlotinib (n = 104)	EGFR inhibitor	57.0	62.0	4.0 months	6.1 weeks	1.04	0.83	19/81
			GEM (n = 103)		57.0	57.0	3.1 months	5.9 weeks		15/85	
Bramhall [40]	2002	III	GEM + marimastat (n = 120)	MMPs inhibitor	58.0	62.0	165.5 days	92.5 days	0.99	0.95	41/59
			GEM (n=119)		60.0	62.0	164 days	96 days		38/62	
Kindler (1) [41]	2012	II	GEM + ganitumab (n = 42)	IGF1R inhibitor	60.0	66.0	8.7 months	5.1 months	0.67	0.65	0/100

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Kindler (2) [41]		II	GEM + conatumumab (n = 41)	Apoptosis inhibitor	59.0	61.0	7.5 months	4.0 months	0.87	0.65	0/100
			GEM (n = 42)		62.0	61.0	5.9 months	2.1 months			0/100
Fuchs (1) [42]	2015	III	GEM + ganitumab (n=318)	IGF1R inhibitor	50.0	62.0	7.0 months	3.6 months	1	1	0/100
Fuchs (2) [42]			GEM + ganitumab (n = 160)		53.0	62.0	7.1 months	3.7 months	0.97	0.97	0/100
Deplanque [43]	2015	III	GEM + masitinib (n = 173)	C-Kit inhibitor	NA	NA	7.7 months	NA	0.89	NA	NA
			GEM (n = 175)		NA	NA	7.0 months	NA			NA
Infante [44]	2014	II	GEM + trametinib (n = 80)	MEK inhibitor	49.0	64.0	8.4 months	16.1 weeks	0.98	0.93	0/100
			GEM (n = 80)		58.0	63.5	6.7 months	15.1 weeks			0/100
O'Neil [45]	2015	II/III	GEM + rigosertib (n = 106)	PI3K inhibitor	65.0	63.2	6.1 months	3.4 months	1.24	0.96	0/100
			GEM (n = 54)		57.0	61.8	6.4 months	3.4 months			0/100
Hong [46]	2014	II	GEM + simvastatin (n = 58)	HMG-CoA inhibitor	62.1	60.0	NA	NA	NA	NA	12/88
			GEM (n = 56)		59.0	56.0	NA	NA			13/87
Wolpin [47]	2013	II	GEM + AGS-1C4D4 (n = 133)	PSCA inhibitor	55.6	62.0	7.6 months	3.8 months	0.78	0.84	0/100
			GEM (n = 63)		30.0	63.0	5.5 months	3.2 months			0/100
Catenacci [48]	2015	Ib/II	GEM + vismodegib (n = 53)	Hedgehog inhibitor	58.0	64.0	6.9 months	4.0 months	0.96	0.83	0/100
			GEM (n = 53)		51.0	64.0	6.1 months	2.5 months			0/100
Heinemann (1) [49]	2013	II	GEM + upamostat (n = 31)	Urokinase inhibitor	64.5	67.0	9.7 months	5.6 months	NA	NA	100/0
Heinemann (2) [49]			GEM + upamostat (n = 33)		36.4	62.0	12.5 months	8.3 months			100/0
			GEM (n = 31)		45.2	59.0	9.9 months	8.2 months			100/0
Borad (1) [23]	2015	II	GEM + TH-302 (n = 71)	Hypoxia-activator	62.0	63.0	8.7 months	5.6 months	0.95	0.66	21/79
Borad (2) [23]			GEM + TH-302 (n = 74)		57.0	65.0	9.2 months	6.0 months	0.86	0.59	27/73
			GEM (n = 69)		58.0	67.0	6.9 months	3.6 months			22/78
Benson (1) [50]	2017	II	GEM + Simtuzumab (n = 79)	IOXL2 inhibitor	63	63	3.7 months	7.6 months	0.83	1.09	0/100
Benson (1) [50]			GEM + Simtuzumab (n = 76)		63	63	3.5 months	5.9 months	1.07	1.13	0/100
			GEM (n = 81)		63	63	3.7 months	5.7 months			0/100

FTase: farnesyl transferase; EGFR: epidermal growth factor receptor; MMPs: matrix metalloproteinases; IGF1R: insulin-like growth factor 1 receptor; HMG-CoA: 3-hydroxy-3-methyl glutaryl coenzyme A; LA/MPC: locally advanced/metastatic pancreatic cancer; NA: not available, GEM: gemcitabine; OS: overall survival; PFS: progression-free survival; LOXL2: lysyl oxidase-like 2.

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**Table 2.** Quality assessment of publications

First author (Year )	Random method	Allocation concealment	Blind	Withdraw description	Identical baseline	Quality level
Friess (2006) [28]	Random-assignment	Central office	Yes	Detailed standards	Yes	A
Spano (2008) [29]	Random-assignment	Central office	No	Detailed standards	Yes	A
Richards (2011) [30]	Random-assignment	Central office	No	Detailed standards	Yes	A
Kindler (2010) [20]	Random-assignment	Central office	Yes	Detailed standards	Yes	A
Kindler (2011) [31]	Random-assignment	Central office	Yes	Detailed standards	Yes	A
Gonçalves (2012) [32]	Random-assignment	Central office	Yes	Detailed standards	Yes	A
Rougier (2013) [33]	Random-assignment	Central office	Yes	Detailed standards	Yes	A
Bergmann (2015) [34]	Random-assignment	Central office	No	Detailed standards	Yes	A
Ioka (2015) [22]	Random-assignment	Central office	Yes	Detailed standards	Yes	A
Yamaue (2015) [35]	Random-assignment	Central office	Yes	Detailed standards	Yes	A
Van Cutsem (2004) [36]	Random-assignment	Central office	Yes	Detailed standards	Yes	A
Eckhardt (2009) [37]	Random-assignment	Central office	Yes	Detailed standards	Yes	A
Senderowicz (2007) [24]	Random-assignment	Central office	Yes	Detailed standards	Yes	A
Moore (2007) [17]	Random-assignment	Central office	Yes	Detailed standards	Yes	A
Philip (2010) [38]	Random-assignment	Central office	No	Detailed standards	Yes	A
Propper (2014) [39]	Random-assignment	Central office	Yes	Detailed standards	Yes	A
Bramhall ( 2002) [40]	Random-assignment	Central office	Yes	Detailed standards	Yes	A
Kindler (2012) [41]	Random-assignment	Central office	Yes	Detailed standards	Yes	A
Fuchs (2015) [42]	Random-assignment	Central office	Yes	Detailed standards	Yes	A
Deplanque (2015) [43]	Random-assignment	Central office	Yes	Detailed standards	Yes	A
Infante (2014) [44]	Random-assignment	Central office	Yes	Detailed standards	Yes	A
O'Neil (2015) [45]	Random-assignment	No description	No	No description	Yes	C
Hong (2014) [46]	Random-assignment	Central office	Yes	Detailed standards	Yes	A
Wolpin (2013) [47]	Random-assignment	Central office	No	Detailed standards	Yes	A
Catenacci (2015) [48]	Random-assignment	No description	No	Detailed standards	Yes	A
Heinemann (2013) [49]	Random-assignment	No description	No	Detailed standards	Yes	B
Borad (2015) [23]	Random-assignment	Central office	No	No description	Yes	B
Benson (2017) [50]	Random-assignment	Central office	Yes	Detailed standards	Yes	A

selected. There was no significant difference in OS between GEM + TA and GEM alone (HR = 0.969, 95% CI: 0.922-1.019,  $P = 0.217$ ) (**Figure 2**). Similarly, no significant difference was demonstrated in the subgroup analysis of single pathway.

### Progression-free survival analysis

Nineteen studies analyzed PFS (HR with 95% CI). The test for heterogeneity of PFS found no significant difference ( $P = 0.070$ ), and thus the fixed effect model was used. There was a significant increase on the PFS when GEM + TA compared with GEM alone (HR = 0.923, 95% CI: 0.876-0.974,  $P = 0.003$ ) (**Figure 3**).

In the subgroup analysis, compared with GEM alone, the PFS was significantly increased in

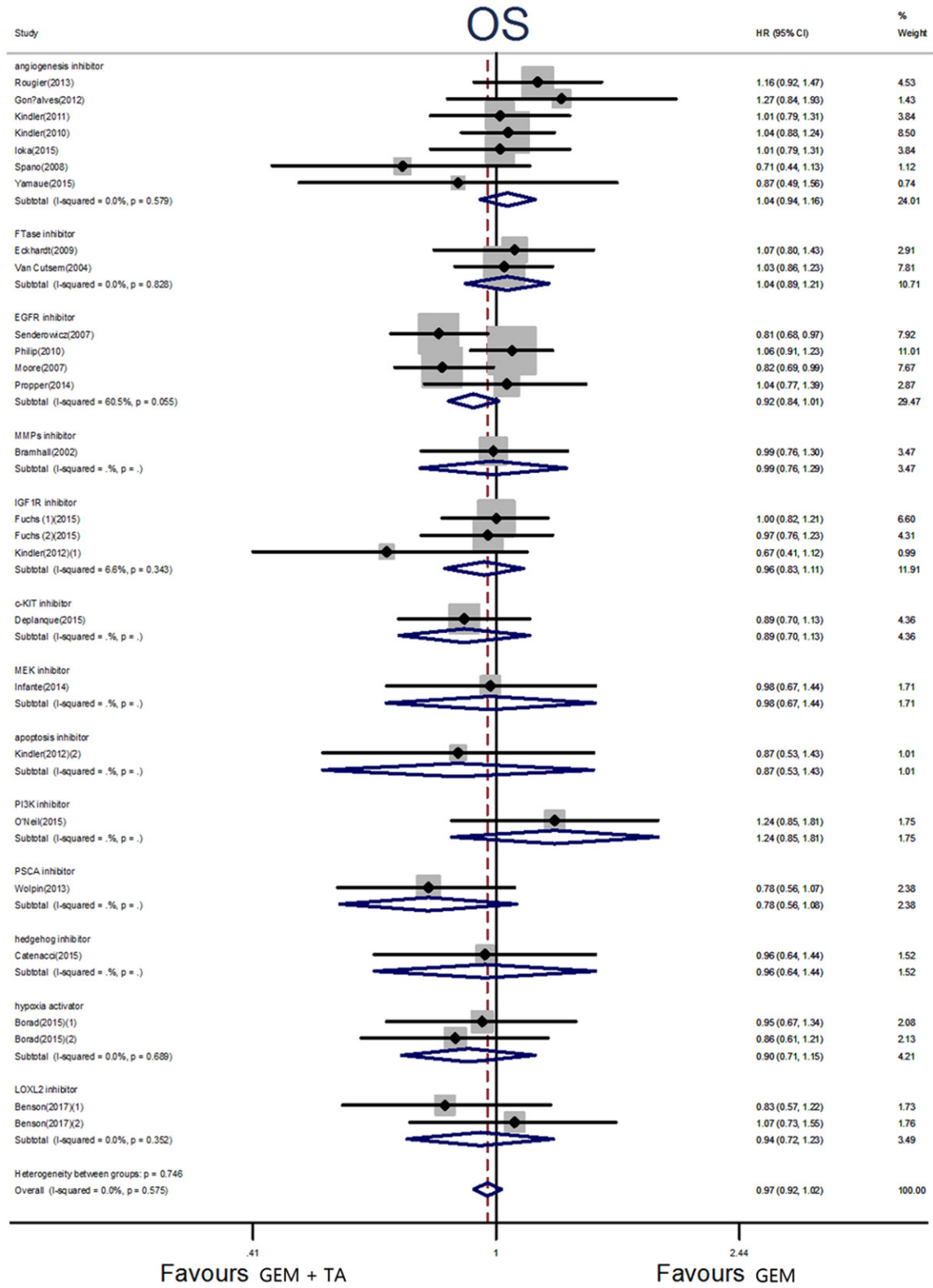
GEM + EGFR inhibitors arm (HR = 0.881, 95% CI: 0.805-0.965,  $P = 0.006$ ) and GEM + hypoxia activators arm (HR = 0.624, 95% CI: 0.474-0.821,  $P = 0.001$ ).

### Overall response rate

Twenty-three studies described ORR. The test for heterogeneity of ORR reported significant difference ( $P < 0.001$ ), and the random-effects model was selected for the meta-analysis. There was no significant difference in OS between GEM + TA and GEM monotherapy (OR = 1.053, 95% CI: 0.799-1.388,  $P = 0.714$ ) (**Figure 4**).

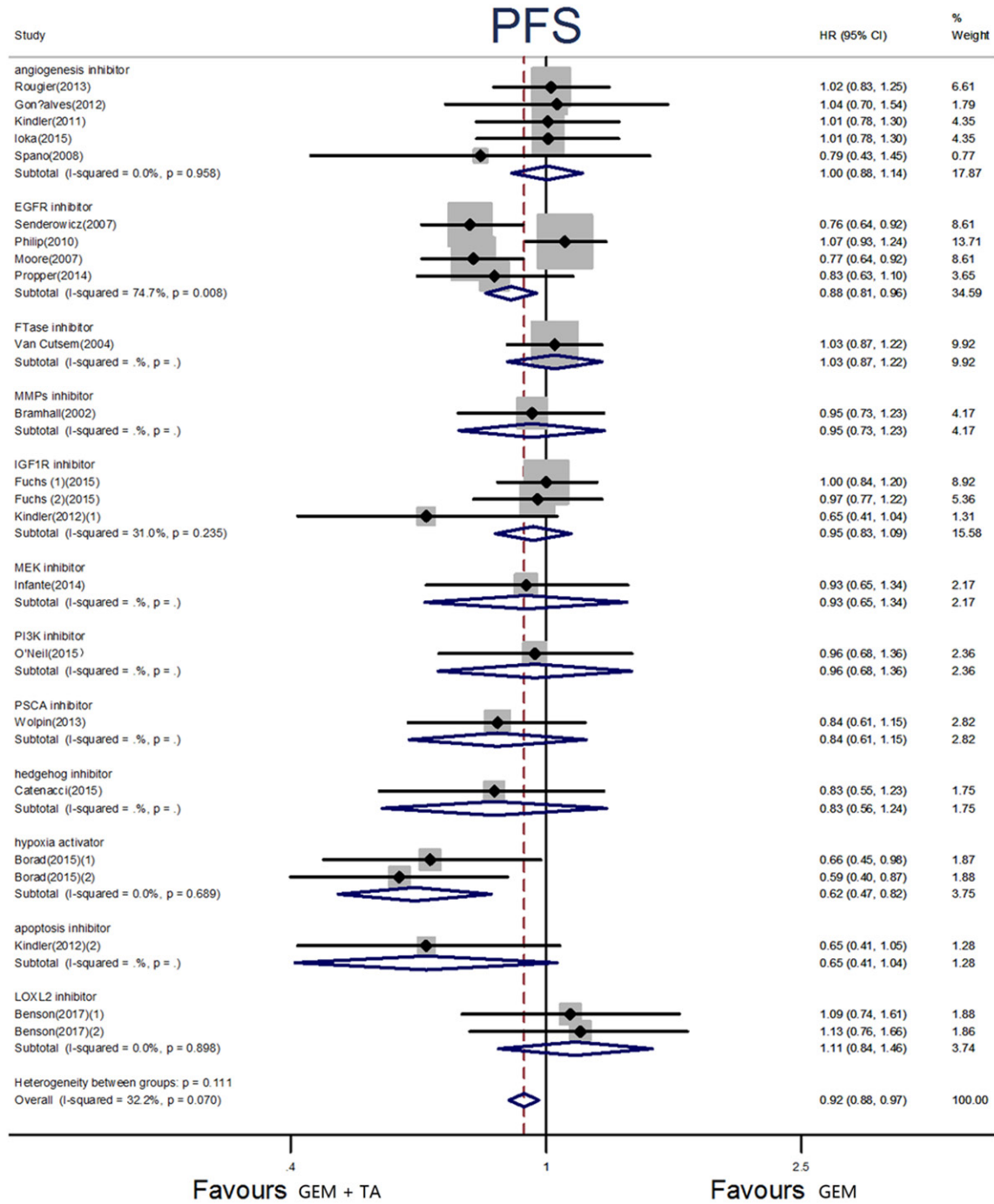
In the subgroup analysis of single pathway, the ORR was significantly improved in GEM + angiogenesis inhibitors arm (OR = 1.631, 95% CI:

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**Figure 2.** Forest plot for comparison of overall survival (OS) between gemcitabine plus targeted agents (GEM + TA) and gemcitabine (GEM) alone therapy.

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**Figure 3.** Forest plot for comparison of progression-free survival (PFS) between GEM + TA and GEM alone therapy.

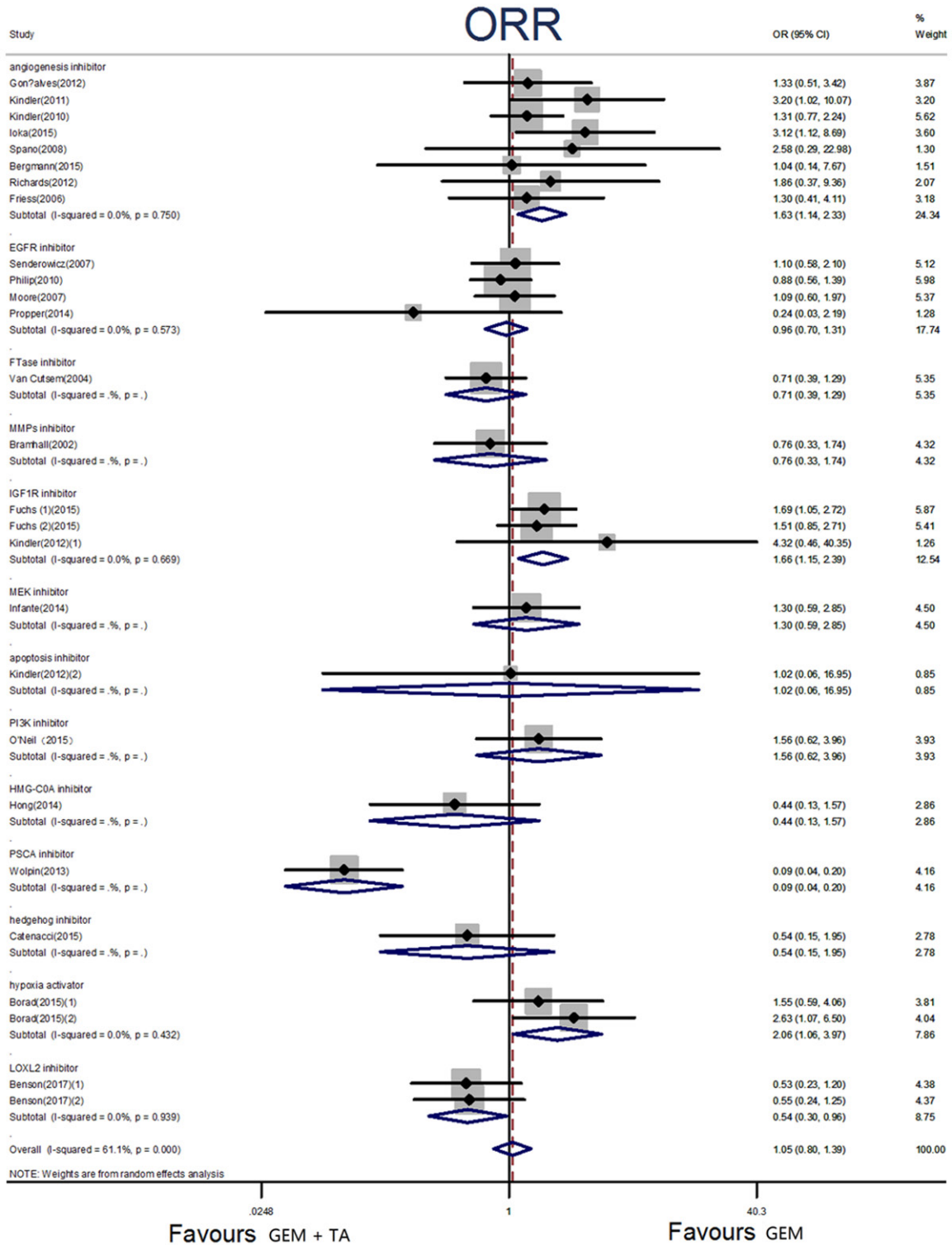
1.143-2.328,  $P = 0.007$ ), GEM + IGF1R inhibitors arm (OR = 1.658, 95% CI: 1.152-2.385,  $P = 0.006$ ) and GEM + hypoxia activators arm (OR = 2.056, 95% CI: 1.064-3.974,  $P = 0.032$ ) compared with GEM monotherapy. However, GEM alone brought significant benefit compared with the GEM + LOXL2 inhibitors arm (OR = 0.540, 95% CI: 0.302-0.964,  $P = 0.037$ ).

### Grade 3-4 toxicity analysis

Grade 3-4 hematologic toxicities and non-hematologic toxicities were extracted from twenty-eight eligible trials (Table 3). There were significant differences in the tests for heterogeneity of anemia, neutropenia and thrombocytopen ( $P < 0.05$ ), therefore the random-effects



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**Figure 4.** Forest plot for comparison of overall response rate (ORR) between GEM + TA and GEM alone therapy.

models were selected in these toxicity analyses. The tests of heterogeneity found no significant difference ( $P > 0.05$ ) in other adverse

events, and the fixed effect models were used. GEM + TA significant increased grade 3-4 neutropenia (OR = 1.220, 95% CI: 1.021-1.459,  $P =$

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**Table 3.** Comparison of grade 3-4 toxicity rates between gemcitabine (GEM) and gemcitabine plus targeted agents (GEM + TA)

Grade 3-4 toxicity	Studies for analysis (n)	Grade 3-4 toxicity/total patients, n/N (%)		OR	95% CI	Significance test	
		GEM + TA	GEM			Z	P
<b>Hematologic toxicity</b>							
Anemia	21	309/3051 (10.1)	229/2758 (8.3)	1.003	0.731-1.377	0.02	0.984
Neutropenia	22	902/3633 (24.8)	646/3017 (21.4)	1.220	1.021-1.459	2.18	0.029
Thrombocytopenia	21	371/3293 (11.3)	230/2651 (8.7)	1.345	1.019-1.777	2.09	0.037
<b>Non-hematologic toxicity</b>							
Nausea	21	205/3537 (5.8)	166/3074 (5.4)	1.137	0.920-1.404	1.19	0.234
Vomiting	22	191/3703 (5.2)	168/3137 (5.4)	1.008	0.817-1.243	0.07	0.941
Diarrhoea	18	120/3441 (3.5)	74/2969 (2.5)	1.438	1.076-1.921	2.45	0.014
Fatigue	21	412/3597 (11.5)	323/3003 (10.8)	1.141	0.979-1.331	1.69	0.092
Rash	9	129/2321 (5.6)	24/2159 (1.1)	6.383	4.082-9.983	8.12	< 0.001

0.029), grade 3-4 thrombocytopenia (OR = 1.345, 95% CI: 1.019-1.777,  $P = 0.037$ ), grade 3-4 diarrhoea (OR = 1.438, 95% CI: 1.076-1.921,  $P = 0.014$ ), and grade 3-4 rash (OR = 6.383, 95% CI: 4.082-9.983,  $P < 0.001$ ) compared with GEM alone. Whereas no significant difference was found in grade 3-4 anemia, nausea, vomiting and fatigue.

### *Risk of bias in selected studies*

No publication bias was detected by using the Egger's test for OS ( $P = 0.463$ ). Funnel plots presented substantial symmetry and exhibited little evidence of publication bias (**Figure 5**).

### **Discussion**

For the last 15 years, targeted agents have obtained the low success rates in the treatment of APC patients compared with other cancers. In our meta-analysis, there was no significant difference in OS or ORR for GEM + TA compared with GEM alone for the treatment of APC patients. Indeed, there was no survival improvement observed for majority of selected molecular targeted drugs. GEM + TA demonstrated a significant, but marginal, gain in PFS (HR 0.923). In the subgroup analysis, the hypoxia activators indicated the advantages in PFS and ORR. The EGFR inhibitors demonstrated the advantage in PFS. The angiogenesis inhibitors and IGF1R inhibitors showed the advantages in ORR. However, GEM alone reported significant value on ORR compared with the GEM + LOXL2 inhibitors.

We reviewed previous meta-analyses which concerned about the efficacy of targeted

agents in patients with APC, and were observed similar findings. The meta-analysis by Li et al. reported that no significant difference was found on OS and FPS between GEM + TA and GEM alone, and its pooled data were retrieved from phase III and phase II trials [51]. Another meta-analysis by Ottaiano et al. indicated that there was no significant gain on OS when GEM + TA versus GEM, and its data were retrieved from phase III studies [52]. However, the targeted agents showed a significant but marginal benefit on PFS in our research. In our meta-analysis, three clinical trials reported positive results on PFS. Two studies by Moore et al. and Senderowicz et al. reported that Erlotinib as EGFR inhibitor brought the advantage on PFS for APC patients [17, 24], and were included in the previous meta-analyses. A study by Borad et al. reported that TH-302 (a kind of hypoxia-activator) plus GEM offered a significant benefit on PFS for APC patients [23]. Our research added new studies compared with the previous meta-analyses. Among these new trials, only TH-302 studied by Borad et al. showed the clinical benefit on PFS, but others failed to find the significant difference. Therefore, that targeted-based therapy showed a significant advantage on PFS was a result of integrated effect of all selected studies.

Altogether, the addition of targeted drugs to GEM did not significantly bring clinical benefits for APC patients. There are three possible reasons for these findings:

Firstly, pancreatic cancers have an average of 63 genetic alterations, and these alterations formed 12 core molecular signaling pathways

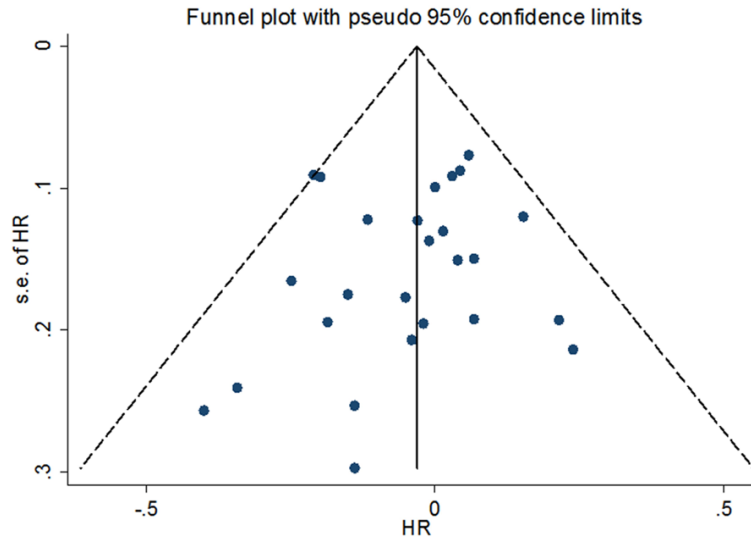


Figure 5. Funnel plot assessing publication bias for overall survival.

that are genetically interacted in 67 to 100% of the tumors [53]. In pancreatic cancer, significant genetic mutations of K-ras and p53, over-expression of heat shock proteins, activation of NFκB, histone deacetylase and the activities of other proteins (COX-2, Nrf2 and bcl-2 family members) are closely associated with apoptotic resistance of the cancer cells [54].

In addition, the characteristics of multiple signaling pathways may provide many therapeutic targets for the treatment of pancreatic cancer, but it also suggests that targeted agent with single pathway may have disappointing efficacy on the therapy of pancreatic cancer. In some selected trials, the posteriori tumor analyses were performed. In the study by Fucks et al., ganitumab (a IGF1R inhibitor) plus GEM failed to bring a treatment effect on OS or PFS compared with GEM alone in the APC patients with high IGF-1 expression, and this result indicated that the high expression of IGF-1 was not linked with a treatment effect in GEM + ganitumab arm [42]. In the study by O’Nail et al., rigosertib (a PI3K inhibitor) added to GEM did not improve the survival of APC patients with P13K-related mutations compared with GEM alone, and the outcomes indicated that there was no correlation between P13K-related mutations and efficacy in GEM + TA arm [45]. In the study by Moore et al. (erlotinib, an EGFR inhibitor) [17] and Philip et al. (cetuximab, a EGFR inhibitor) [38], no significant difference was found on OS between GEM + TA and GEM in the APC patients

with EGFR positive. Ottaiano et al. pooled the HR from the patients with EGFR positive in these two studies, and confirmed the absence of correlation between EGFR expression and efficacy in the GEM + TA arms [52]. Significantly, there was no significant difference on OS in the study of masitinib (a c-Kit inhibitor) by Deplanque et al., however the significant benefits were observed in ‘ACOX1’ subgroup (HR = 0.23, 95% CI: 0.1-0.51,  $P = 0.001$  and ‘Pain’ subgroup (HR = 0.62, 95% CI: 0.43-0.89,  $P = 0.012$ ) [43]. These results suggested that masitinib plus GEM could

improve efficacy of APC patients with ACOX1 and pain expression compared with GEM alone. Therefore, that the molecular biomarkers were not investigated for the APC patients might be a further reason for disappointing outcomes of clinical trials.

Finally, only few trials were currently designed on targeted-based treatment, and thus our meta-analysis included targeted drugs with different mechanisms of action. Which probably results in that the research samples of enrolled patients were not enough, and survival advantages of targeted agents from some literatures will be exaggerated, and those from some literatures will be underestimated.

Moreover, the safety of targeted drugs is a concern of the clinician. Our meta-analysis revealed that grade 3-4 neutropenia, thrombocytopenia, diarrhoea and rash were significant increased in the targeted therapy arms, and most of these toxicities were prospective and reversible in treatment. Among them, there was a high incidence of rash associated with targeted therapies. The major clinical manifestation of rash is an eruption of papules and pustules, typically appearing in face, scalp, upper chest and back, and needs to be identified and managed actively [55].

### Conclusion

Based on the outcomes of this analysis, targeted agents plus GEM did not improve the OS and

ORR in APC patients, and can significantly, but marginal, increase the PFS in APC patients. Regarding the great clinical benefits brought by targeted therapy in other solid tumors, more clinical trials were expected to design for further investigating the efficacy and value of targeted agents for APC patients.

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### Disclosure of conflict of interest

None.

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